Exhibit A

Remington's Pharmaceutical Sciences

18

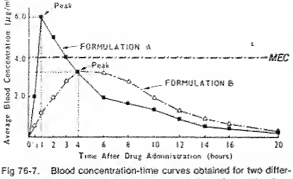

Fig 76-7. Blood concentration-time curves obtained for two different formulations of the same drug demonstrating relationship of the profiles to the minimum effective concentration (*MEC*).

centrations following equal doses of two different formulations of the same cardiac glycoside, and 4 μg/mL now represents the minimum toxic concentration (*MTC*) and 2 μg/mL represents the *MEC* (Fig 76-8). Formulation *A*, although effective, may also be toxic, while Formulation *B* produces concentrations well above the *MEC* but never achieves toxic levels.

Time of Peak Concentration—The second parameter of importance is the measurement of the length of time necessary to achieve the maximum concentration after drug administration. This time is called the time of peak blood concentration. In Fig 76-7, for Formulation *A* the time necessary to achieve peak blood concentration is 1 hr; for Formulation *B* it is 4 hr. This parameter is related closely to the rate of absorption of the drug from a formulation and may be used as a simple measure of rate of absorption.

To illustrate its importance, suppose the two curves in Fig 76-8 now represent two formulations of an analgesic and that in this case the minimum effective concentration is 2 μg/mL. Formulation *A* will achieve the *MEC* in 30 min; Formulation *B* does not achieve that concentration until 2 hr. Obviously, Formulation *A* would then produce analgesia much more rapidly than Formulation *B* and would probably be preferable as an analgesic agent. On the other hand, if one were more interested in the duration of the analgesic effect than on the time of onset, Formulation *B* would present more sustained activity, maintaining serum concentrations above the *MEC* for a longer time (8 hr) than Formulation *A* (5½ hr).

Area Under the Concentration-Time Curve—The third, and sometimes the most important parameter for evaluation, is the area under the serum, blood or plasma concentration-time curve (AUC). This area is reported in amount/volume × time (eg, μg/mL × hours or grams/100 mL × hours, etc) and can be considered representative of the amount of drug absorbed following administration of a single dose of the drug.

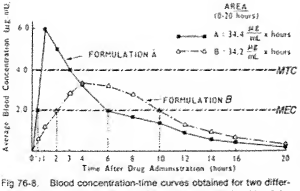

Fig 76-8. Blood concentration-time curves obtained for two different formulations of same the drug demonstrating relationship of the profiles to the minimum toxic concentration (*MTC*) and the minimum effective concentration (*MEC*).

Returning to Fig 76-8, the curves, although much different in shape, have approximately the same areas (*A* = 34.4 μg/mL × hours; *B* = 34.2 μg/mL × hours) and both formulations can be considered to deliver the same amount of drug to the systemic circulation. Thus, one can see that AUC does not represent the only criterion on which bioequivalency can be judged. All the results, as a composite, must be used in reaching a decision as to bioequivalency; no one parameter serves this purpose.

Statistical Sense and Nonsense—When statistical evaluations are employed in bioequivalency testing one must be careful not to assume, from a statement that "no statistically significant differences were detected," that two drug products are, therefore, bioequivalent. The basis of most tests for statistically significant differences is that the two products are assumed to be the same until proven otherwise. Therefore, if the data presented are highly variable (large standard deviation, ie, wide range of values), it would be possible to show that there was no statistically significant difference between an AUC of 100 units (%) versus an AUC of 40 units (%). In this case the statistical test does not indicate that the AUCs are truly similar; it simply means that the data were too variable from patient to patient for the statistics to be able to detect a 60-unit (%) difference in areas, even if it existed.

There are two types of errors associated with any statistical test. These are:

1. **Alpha (*α*) Error**—This is the error with which most people are familiar and is the error associated with the statement, "The data have been analyzed statistically." *α* error is the probability (defined by the *p* value) by saying the two treatments are different when in fact they are the same. It should be noted that while highly significant *p* values reduce the alpha error, they provide no indication of the possibility that the two treatments being called the same when in fact they are different.
2. **Beta (*β*) Error**—This is the error associated with the possibility of calling two treatments the same when in fact they are different. As the maximum percent difference between means which can be detected with an *α* error of $p \leq 0.05$ is reduced, the *β* error also is reduced. This increase in statistical sensitivity (reduced *α* and *β* error) is obtained by reducing the variability of the data. Variability usually is reduced by increasing the number of data points (subjects) in a bioavailability study. It is implicit that the analytical methodology is specific, sensitive and precise.

The objective of statistical testing for bioavailability evaluation should be to minimize both the *α* and *β* error. Since both errors are related mathematically to the variability of the data collected, the solution is relatively simple. Sufficient data should be gathered so that the general statistical test (*α* error test) would detect, if it existed, a predetermined percent difference (20% for example) between the two dosage forms. If, for example, the two treatments are found statistically not to be ($p \leq 0.05$) different significantly, the results indicate that there is only 1 chance in 20 that the treatments are claimed to be different when in fact they are the same.

If there were 18 subjects in the above example and a 20% difference would have been significantly different statistically, there would be a *β* error of 4 chances in 20 that a 25% difference between means was not detected. That is, that treatments which differed by more than 25% were claimed to be the same when in fact they were different. The level of statistical sensitivity which one feels is adequate (20% as a rule of thumb) must be reevaluated for each drug product tested based on the clinical performance of the drug.

Statistical analysis also can go to the other extreme. For example, tests might show that an AUC of 100 units (100%) was statistically significantly different from an AUC of 90